A STAFF REPORT

For the Use of the Subcommittee on Oversight and Investigations
In Preparation for Its Hearing,

"Human Tissue Samples: NIH Research Policies and Practices," June 13-14, 2006

This staff report was written by the Majority and Minority Committee staff of the House Committee on Energy and Commerce.

Background

Human tissues are biological materials defined as "including everything from subcellular structures like DNA, to cells, tissue (bone, muscle, connective tissue, and skin), organs (e.g., liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail clippings, shed epithelial cells, placenta)."[1] For purposes of the Subcommittee's inquiry, this report focuses on biological materials most frequently used in biomedical research such as tissues and cells. These are raw biological materials extracted from human beings that are to be distinguished from the biological inventions derived from such samples. These extracted tissues are stored and generate portions of tissues called samples.

Ever since 1858 when Rudolf Virchow wrote his famous book that detailed how changes in cells accounted for diseases in organs, human tissue samples have been the foundation of biomedical research.[2] In its 1999 report, the RAND Corporation published a "conservative estimate" that more than 307 million tissue samples from more than 178 million people were stored in the United States.[3] This number was reportedly increasing by more than 20 million samples a year. [4] Tissue samples have played a central role in major studies such as the Framingham studies on heart disease and the Women's Health Initiative (WHI), one of the largest women's health studies in which over a 15-year period, 161,000 women gave blood, urine, and other samples to investigators.[5] Human tissue samples also have significant value to biotechnology and pharmaceutical companies because these materials "can help them: reduce drug development times; develop new therapies and drugs; react quickly to unexpected adverse reactions; and identify new assay techniques or biomarkers."[6]

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[1] Eiseman, E. and Castillo, J., Handbook of Human Tissue Sources, RAND Monograph Report, 7 (1999). See also U.S. Congress, Office of Technology Assessment, New Developments in Biotechnology: Ownership of Human Tissues and Cells – Special Report, OTA-BA-337 (March 1987) at 3.
[2] Hakimian, R. and Korn, D., "Ownership and Use of Tissue Specimens for Research," Journal of the American Medical Association, November 24, 2004, at 2500.
[3] Eiseman, E. and Castillo, J., Handbook of Human Tissue Sources, RAND Monograph Report,xvii (1999).
[4] Id. The National Bioethics Advisory Commission (NBAC) estimated that as of 1998, more than 282 million specimens of human biological materials were stored in the United States, accumulating at a rate of more than 20 million cases per year.
[5] Hindin, T., "Technology and Clinical Trials," Applied Clinical Trials, April 2006 at 12.
[6] Mills, J.F., "Precedents for Good Storage Practice," Applied Clinical Trials, April 2006 at 58.

The issue of human tissue samples has assumed greater importance at the National Institutes of Health (NIH) and strengthened the need for more guidance to NIH-funded institutions (NIH's extramural research program that are more than 80 percent of the NIH's budget) as well as for the Institutes and Centers at the NIH that conduct their own research (NIH's intramural research program). As noted by the NIH's Director of the Office of Science Policy to NIH staff: "[H]uman specimen repositories and the use of human specimens and data are becoming an increasingly important part of our efforts to advance basic science research and translate discoveries into improved medical care. However, the lack of consistency in the regulations, policies and procedures governing this type of research is creating confusion and barriers for researchers, repository managers, IRB [Institutional Review Board] staff, and their institutions. The magnitude of these challenges will likely grow as advances in informatics make it possible to make human datasets of unprecedented size and scope widely available to the research community."[7] In response to these perceived challenges and as part of the NIH Roadmap, the NIH is coordinating "a high priority effort to develop trans-NIH policies to govern NIH funded research with human specimens and data and to work across government to promote more consistent policies in this area."[8]

The focus of the inquiry for this hearing is the collection, storage, tracking, and use of human tissue samples in the NIH intramural research program.

The Committee's investigation in this area was prompted in part by concerns raised by Susan Molchan, M.D., Program Director for Alzheimer's Disease Research at the National Institute of Aging (NIA), to Committee staff in April 2005. Dr. Molchan had been a clinical researcher interested in Alzheimer's disease research at the National Institute of Mental Health (NIMH). From 1993 to 1995, she conducted a small clinical trial involving the collection of spinal fluid from about 25 people (some patients with Alzheimer's disease and some normal volunteers) and the use of lithium as a probe for potential biomarkers of Alzheimer's disease in spinal fluid and blood. In early 1997, Dr. Molchan left the NIMH, but she had not finished this study. She had published two papers and used at the very most 20 percent of the spinal fluid collected. The unused spinal fluid remained stored in freezers at the NIMH Geriatric Psychiatry Branch. The Chief of the Geriatric Psychiatry Branch was Trey Sunderland, M.D., who assumed control of the spinal fluid samples after Dr. Molchan left NIMH.

At a hearing on June 22, 2004, the Subcommittee on Oversight and Investigations revealed that Dr. Sunderland had received over $500,000 in payments from Pfizer during 1999-2004 for outside consulting and speaking without any record of prior approval for these activities or disclosure in his government financial-report filings.

By the fall of 2004, Dr. Molchan had been back at the NIH for three years, this time at the National Institute of Aging. At a meeting of top scientists and researchers,

[7] Email on "Harmonization and Repositories," from Lana R. Skirboll, Ph.D., Director, Office of Science Policy, NIH, October 27, 2005 to various NIH staff.
[8] Id.

she learned that an outside researcher was pursuing funding for a lithium study similar to the one that Dr. Molchan had been unable to complete at NIMH. Spinal fluid samples are extremely valuable and very difficult to obtain. The outside researcher was very interested in getting Dr. Molchan's assistance in obtaining the spinal fluid samples and the linked clinical data from her study. Dr. Molchan agreed to assist. In the fall of 2004, Dr. Molchan asked Dr. Sunderland about the samples. After two months of inquiries, Dr. Sunderland sent two 0.5 cc samples from 10 subjects (about 2-3 percent of the unused amount of spinal fluid) to the outside researcher. In March 2005, Dr. Molchan asked Dr. Sunderland about the linked clinical data. Dr. Sunderland told her that that the data had been purged because it was over 5-7 years old and subject to purging.

Dr. Molchan was concerned about what happened to the more than 95 percent of the unused spinal fluid samples left in the freezer and to the data. In particular, after the public reports about Dr. Sunderland's undisclosed activities with Pfizer, she was concerned that Dr. Sunderland might have inappropriately or improperly diverted spinal fluid samples from her lithium study to Pfizer as part of his financial relationship. She pursued her concerns for several weeks during March-April 2005 through various NIH channels and with the Office of Inspector General (OIG), Department of Health and Human Services (HHS). In April 2005 she contacted staff with the Committee on Energy and Commerce.

In investigating her concerns and in general about the relevant NIH policies, the Committee staff learned from NIH officials that NIH had no uniform, centralized, and mandatory authority regulating the handling of human tissue samples. Some NIH laboratories kept a written record on the maintenance of these samples, but other NIH laboratories did not. Although there were explicit regulations defined in 42 C.F.R. 72.6 detailing the handling for hazardous biological materials and select agents, there was no explicit policy for the handling and accounting of human tissue samples. In addition, there was no formal inventory control or tracking system at NIH. If a freezer or other storage facility malfunctions and the human tissue samples become unusable, NIH laboratories were not required to account for the disposition of these samples. There was reason to believe that there were cases where NIH lost human tissue samples but had no record of what had been lost. Moreover, the lack of accountability left NIH wholly vulnerable to theft and diversion of valuable human tissue samples. These preliminary inquiries raised serious concerns over what was described to Committee staff by NIH officials as a fairly loose, ad-hoc approach to controlling human tissue samples.

On June 20, 2005, the bipartisan leadership of the full Committee and the Subcommittee sent a letter to the Director of the NIH requesting records and information on how human tissue samples are obtained, stored, tracked, and used in intramural programs throughout the institutes and centers of the NIH.[9] In the context of this

[9] The current total number of tissue samples at the NIH is unknown. As the NIH wrote to the Committee in a letter dated August 15, 2005:

"NIH does not maintain a central listing of all tissue samples in its possession. Each laboratory is responsible for storing and tracking all samples within its possession. NIH requires that each investigator

investigation, the Committee focused primarily on spinal fluid samples and blood samples obtained from patients and other people participating in NIH intramural clinical trials.

One subject area of the Committee's June 20, 2005, request concerned the disposition of spinal fluid samples from patients with Alzheimer's disease and control subjects collected by scientists at the National Institute of Mental Health (NIMH) to be used in studies involving lithium. After the NIH's August 15, 2005, production, the Committee staff alerted the NIH that it appeared that not all responsive documents concerning these samples and Dr. Molchan's lithium study had been provided to the Committee. After the Committee staff raised these concerns with NIH about the production, the Committee did receive additional responsive records: three sets of records over the last few months from the NIH related to the spinal fluid samples and the lithium study, with the last set received on January 4, 2006. The Committee was troubled that the NIH did not produce all the responsive records in the first production, and produced these records only after Committee staff pressed several times for these additional responsive records. Most importantly, an NIH document received by the Committee in early 2006 documented that the Geriatric Psychiatry Branch (GPB) had sent spinal fluid samples to Pfizer from 538 subjects, who had participated in 14 different studies at NIMH. (See Exhibit 26) The protocol numbers listed on the documents showed that spinal fluid had been sent to Pfizer from subjects who had participated in Dr. Molchan's lithium study. That fact had not been previously disclosed to either Dr. Molchan or to the Committee.

On January 24, 2006, the bipartisan leadership of the Committee and the Subcommittee sent a letter to NIH requesting additional records about the disposition of the spinal fluid samples, the nature of NIMH oversight over human samples, and the way NIH/NIMH handled the Committee's request for records relating to the lithium study. In addition, on January 24, 2006, the bipartisan leadership of the Committee and the Subcommittee sent a letter to Pfizer, requesting records that could help determine the relationship, if any, between the disposition of the spinal fluid samples in question and Dr. Sunderland's official and/or private consulting activities with Pfizer.

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obtaining such samples complete a Human Pathogen Registration Document, [ ], which requires information on the principal investigator, the location of the work, the agent or human blood, body fluid or tissue being worked with, and the names of all individuals working with the particular material being registered. The document does not require the investigator to supply the number of samples that he/she plans to work with or obtain. NIH currently has 390 Human Pathogen Registration Documents on file for human blood, body fluids, and/or tissues. Currently, 663 laboratories maintain human blood, body fluids, and/or tissue samples. [footnote omitted]. A total of 2340 employees are registered for work involving human blood, body fluids, and/or tissues. It is important to note that these numbers apply only to active research protocols.

In addition, NIH maintains biorepositories to provide investigators with pathological samples for research uses. Two are maintained by the National Cancer Institute, . . . "

Methodology

To review these issues related to human tissue samples, the Committee staff conducted extensive interviews with officials from NIH, former officials with NIH, officials with Pfizer, former officials with Pfizer, and other individuals.[10] Staff reviewed documents obtained by the Committee from NIH and Pfizer. Staff also reviewed public information and records.

NIH's Internal Investigation

The NIH's Office of Management Assessment (OMA) conducted an internal investigation of Dr. Sunderland's outside activity discrepancies first revealed in substantial part at the Subcommittee's June 22, 2004, hearing. The OMA found that Dr. Sunderland engaged in serious misconduct, in violation of HHS ethics rules and Federal law and regulation. The OMA confirmed that there was no documentation for Dr. Sunderland seeking prior approval or reporting the Pfizer activities. After the revelations of the Pfizer activities, Dr. Sunderland self-reported additional activities with other drug or biotech companies that lacked required documentation in which his payments almost totaled $200,000. Dr. Sunderland claimed that these were paperwork violations and that his outside activities did not constitute conflicts of interest with his official duties. In particular, Dr. Sunderland contended that his outside consulting did not relate to his official duty collaboration with Pfizer, which involved the sharing of spinal fluid samples under an April 1998 Material Transfer Agreement (MTA). However, the Ethics Review Panel convened by NIH in April 2005 found a direct overlap between the subject matter of Dr. Sunderland's official area of research and the scientific subject matter of his Pfizer consultancies. In addition, the Panel expressed concern over the 1998 MTA that Dr. Sunderland entered into with Pfizer while he maintained an ongoing consulting relationship with the company in the same area. In addition, in a memorandum dated October 12, 2005, the NIH Ethics Panel found that Dr. Sunderland's official duties constituted an overlap with some of unapproved outside activities with other drug companies he self-reported. (Exhibit 35)

On September 24, 2004, NIH referred an allegation to the Office of Inspector General - HHS (OIG) that Dr. Sunderland may have conducted outside activities during Government work hours without charging leave. Other records in connection with Dr. Sunderland beyond the issue in the referral have also been forwarded by NIH to the OIG.

Committee's Investigation

It should be noted that the NIH investigated Dr. Sunderland's failure to obtain prior approval and disclose outside activities. NIH did not investigate the details of the underlying outside activities at issue. The concerns raised about human tissue samples

[10] Committee staff requested numerous times to interview Dr. Sunderland, but through his attorneys he declined to be interviewed.

led the Committee to investigate issues that arose from Dr. Sunderland's transfers of human tissue samples to Pfizer and examined the details of Dr. Sunderland's two principal consulting arrangements with Pfizer. This staff report is a preliminary report to assist the Members of the Subcommittee on Oversight and Investigations in preparing for the hearings to be held on June 13 and 14, 2006.

Question One: Did Dr. Sunderland obtain personal financial benefits from outside activities (with no record of disclosure to NIH or approval by NIH) with Pfizer, Inc., in any way because of actions he took in his official capacity in facilitating the transfer to Pfizer of human spinal-fluid samples and plasma samples, which were the assets and property of NIH?

Finding/Supporting Evidence: Yes. Records and interviews provide reasonable grounds to believe that Dr. Sunderland personally received $285,000 in compensation from Pfizer for activities that were derived directly from his official acts in providing Pfizer access to spinal fluid samples and plasma samples (over 3000 tubes of NIH property and linked clinical data) and that Dr. Sunderland used NIH employees and resources to provide such access.

Discussion:

The Committee's inquiry focused on the consulting agreements involving Dr. Sunderland's collaborations with Pfizer using human tissue samples procured from his Geriatric Psychiatry Branch in the National Institute of Mental Health (NIMH). Records from Pfizer show that the transfer of spinal fluid samples from Dr. Sunderland's branch at NIMH to Pfizer under an April 1998 Material Transfer Agreement coincided with the initiation of a two-year consulting agreement related to Dr. Sunderland's advice on information generated from those samples. The MTA and the consulting agreement were part of the same scientific collaboration. This consulting agreement and a spin-off consulting agreement from the collaboration netted Dr. Sunderland a minimum of $25,000 per year plus $2,500 per day for each one-day meeting (1998-2003). According to Pfizer, payments under these two contracts totaled $285,000, exclusive of reimbursement of travel expenses.[11]

Dr. Sunderland had been collecting human tissue samples and the related clinical information from NIH Alzheimer's disease patients and their families and controls since the early 1980s. This longitudinal collection of spinal fluid and blood samples was unique. While it was possible to purchase spinal fluid samples from Alzheimer's disease patients, individuals interviewed by Committee confirmed it was unlikely that anywhere

[11] The consulting payments were in addition to sums Pfizer paid Sunderland for speeches or discussions with potential prescribers of Aricept and the occasional advisory board participation. Those payments added an additional $311,000 over roughly the same period of time as the consulting agreements. While such payments are now not permitted under the ethics rules, a special NIH ethics panel concluded that had Dr. Sunderland requested approval for these speeches, they would have been approved under the standards that predated the Committee's investigation and resulting reforms.

but at the clinics of NIH could this unique historical collection of human tissue samples be assembled. Dr. Sunderland collected not only human tissue samples from Alzheimer's disease patients but also samples from their blood relatives as well as samples from controls.

The longitudinal aspect included in this collection gave the samples their unique character. At least some of the subjects had samples drawn both before and after the onset of Alzheimer's disease. Interviews and records obtained from Pfizer provide reasonable grounds to believe that obtaining these spinal fluid samples together with their clinical histories was a primary reason for Pfizer's interest in collaborating with Dr. Sunderland.

The samples themselves and the linked clinical data associated with these samples are generally considered to be valuable assets because such samples can be used for diagnostic, therapeutic, research, and commercial purposes. NIH has told the Committee that it takes the position that tissue samples are the property of the U.S. Government to the extent that NIH asserts an exclusive right to control the disposition and distribution of that material.[12] That would seem to be the case where the NIH has exclusive possession and control of the samples through its storage of these materials in its freezers in its own buildings, all funded by U.S. taxpayers. NIH continually asserts its ownership interests in such samples through its technology transfer policies and legal contracts such as Material Transfer Agreements (MTAs) and Cooperative Research and Development Agreements (CRADAs). In addition, the NIH-1884 form "Request for shipment" used to ship tissue samples to Pfizer noted that they were shipments of government-owned property. (See Exhibit 22)

Three legal documents were involved in the transfer of invaluable human tissue samples and the collaborative research that resulted: a material transfer agreement (MTA) between NIH and Pfizer signed by Dr. Trey Sunderland and two consulting contracts between Pfizer and Dr. Sunderland.

A material transfer agreement is to be distinguished from a collaborative research and development agreement (CRADA) and a consulting agreement involving the scientist and a company independent of the NIH. In a scientific endeavor such as the Pfizer/Sunderland collaboration, according to some NIH officials interviewed by Committee staff, a CRADA would have been the appropriate legal umbrella for this kind of research. (This is discussed in more detail later in this report.) Not only would that arrangement spell out the contributions and obligations of both parties, but it also would spell out the distribution of data and intellectual property rights between the government and the private sector firm, in this case Pfizer. Had a CRADA been negotiated, Dr. Sunderland would not have been able to receive any outside income for his efforts in the collaboration as it would have been part of his official duties.

[12] In an attached response to an e-mail dated May 12, 2006, from NIH staff to Committee staff, NIH stated: "Where have tissue samples sitting in a freezer that have been collected from patients in an intramural trial, whom do these samples belong to? Still belong to the donor? NIH? Lab scientist? Government? If it does not belong to the government, want explanation of why not.

Tissue samples collected within the intramural program belong to the Federal Government."

Although NIH policies on technology transfer mechanisms were evolving and unclear in 1998, according to an NIH official interviewed by Committee staff, because the transfer involved a commercial entity, it is unlikely Pfizer could have taken possession of the samples of this value without a document authorizing the transfer. Absent a CRADA, an MTA was the instrument that specified the terms under which the NIH would release human tissue samples for a specific research purpose. The MTA did not obligate Pfizer to share the resulting data with NIH nor did it specify that the government retained any intellectual property right to the fruits of the proposed research.

Based on its past investigations of NIH scientists' outside consulting agreements, Committee staff believes that Pfizer would not have entered into a scientific collaboration with Dr. Sunderland or any other scientist without a private contract that contained two critical clauses: confidentiality and the right of Pfizer to all intellectual property created as a result of the collaboration.

In a CRADA, Pfizer would not have retained exclusive rights to the data or any patents. Dr. Sunderland would have been precluded from any outside income from the collaboration, if there had been a CRADA such as the one he had executed with Abbott Labs in 1989 in transferring 115 spinal fluid samples. (Exhibit 28)

In this regard it is important to note that Dr. Sunderland is listed as a co-inventor with Pfizer researchers on patents filed in Europe and here in the US relating to the April 1998 MTA.[13] (Exhibit 29) Dr. Sunderland executed at least one assignment of his patent rights to Pfizer as did his co-inventors as was required by his contract of June 10, 1998, and as is typical of discoveries made while on a private payroll. (Exhibit 30) The United States is not an assignee.

In 1997 Pfizer entered into a collaboration with a British firm, Oxford Glycosciences (OGS), to identify unknown biomarkers that would signal the onset of Alzheimer's disease using a proprietary OGS proteomics technology. Dr. David Friedman, the lead Pfizer researcher on the project, began courting Dr. Trey Sunderland in an attempt to obtain access to the NIH human tissue samples in the fall of 1997.

In his interview with Committee staff, Dr. Friedman said he came to understand the significance of the depth of Dr. Sunderland's expertise in his early discussions. On February 20, 1998, Dr. Friedman, and three other Pfizer scientists visited Sunderland's lab at NIMH. A Pfizer e-mail documenting the visit stated: "In discussions regarding Pfizer's needs and Sunderland's needs, Trey indicated that he was very happy with an MTA arrangement plus consulting that Kathy [Smith] has been discussing. Trey was also very interested in publication in a reasonable time frame and that he wanted to make sure that authorship would be based on scientific and intellectual contributions. We indicated agreement on both matters."

[13] Committee understands from NIH that the NIH has recently made a referral to the OIG-HHS on this issue of undisclosed patent applications.

A month later, at the suggestion of Dr. Sunderland, Kathryn Monaghan (now Smith), a Pfizer manager, called Kathy Conn, the tech transfer official at NIMH, about using an MTA to transfer spinal fluid samples. Ms. Monaghan believed that this phone call reflected NIH's agreement to proceed with the material transfer agreement and that they can "work out the CRADA vs. Consult part in due course." (Exhibit 31)

On April 6, 1998 Kathy Monaghan faxed the final version of the MTA to Dr. Sunderland and informed him that the deal with OGS had been finalized. (Exhibit 2) However, Ms. Conn informed the Committee staff that she was unaware that the final MTA had been executed.[14] Records and Committee staff interviews of the individuals involved revealed that neither the Director of NIMH nor the NIMH Scientific Director, the two supervisors of Dr. Sunderland, had knowledge of the transfer of the uniquely valuable samples or were informed of the MTA negotiations. On April 8, 1998, Dr. Sunderland signed the MTA to transfer coded clinical samples of spinal fluid and the accompanying data from over 250 subjects to Pfizer. Six days later, Dr. Barrie Hesp signed the MTA for Pfizer.

In a letter dated April 20, 1998, Pfizer sent Dr. Sunderland at NIH the signed copy of the MTA with a note that indicated that they expected the samples to be shipped mid-May (Exhibit 1) Dr. Sunderland was then sent a "draft consulting agreement" to his home in a letter dated on the same day. (Exhibit 5) A two-year consulting agreement that Pfizer labeled the "OGS" agreement was signed by Dr. Hesp (dated June 10, 1998) and Dr. Sunderland (dated June 18, 1998) effective May 1, 1998. (Exhibit 7) It provided for a consulting payment to Dr. Trey Sunderland of $25,000 per year and $2,500 per day for each meeting plus expenses. This agreement was renewable for two-year periods, and was renewed two more times.

It should be noted that this consulting agreement required that Dr. Sunderland transfer any interest he may have in the research arising from the agreement with Pfizer as he subsequently did with the patent assignment. (Exhibit 7) Dr. Sunderland also agreed not to "disclose confidential information for so long as it remains unpublished…"

Only after the consulting agreement was signed were the samples finally shipped from NIH. According to Dr. Friedman in his interview with Committee staff, on or around June 24, 1998, Drs. Friedman and Sunderland accompanied 621 tubes to OGS in Britain. But Dr. Sunderland did not deliver the clinical data associated with the samples until August 1998. Emails indicate Pfizer officials were quite upset about the delay because the associated clinical information made these samples useful for the intended research and this delay would affect the pace of the research. (Exhibit). Pfizer calls this research project involving NIMH and OGS the "unknown biomarkers" project.

By the end of July 1998, Pfizer and Sunderland decided to pursue a second collaboration regarding the validity of already "known biomarkers," a beta and tau. (Exhibit 8) The NIH spinal fluid samples were to be used for this project as well. This

[14] As discussed later, Ms. Conn believed that the next step in the process was Pfizer sending her a copy of the MTA to review. This matter is discussed in more detail later in the report.

second project resulted in a second separate consulting agreement for Dr. Sunderland but not a new MTA for the transfer of NIH samples for this separate and new Pfizer research project. The second consulting agreement was signed by Dr. Hesp for Pfizer with an October 6, 1998, date and by Dr. Sunderland with an October 12, 1998, date. On February 9, 1999, the shipment of spinal fluid samples from NIH to Pfizer for the "known biomarkers" project began.

According to records and information, approximately 3,200 tubes of spinal fluid and 388 tubes of plasma were shipped to Pfizer in connection with both biomarker projects.[15] (See Slide 5) Of these, 2,200 or so were for the "known biomarkers" project and the remaining 1,100 were for the "unknown biomarkers" research. The spinal fluid samples linked with the well-characterized clinical data are invaluable tools for scientific research. Based on available records, the NIH only had data on the 2,132 tubes shipped in connection with the "known biomarkers" project. The Committee staff has reasonable grounds to conclude that NIH did not have knowledge of the more than 1,000 tubes of spinal fluid shipped pursuant to the "unknown biomarkers" agreement.

Question Two: Does the available evidence provide reasonable grounds to believe that Dr. Sunderland and others omitted important information, or provided inaccurate information, about the circumstances surrounding Dr. Sunderland's collaborations with Pfizer, Inc. that involved the human samples provided by Dr. Sunderland?

Finding/Supporting Evidence: Yes. While Dr. Sunderland refused invitations to be interviewed by the Committee, records and interviews provide reasonable grounds to believe that some of Dr. Sunderland's statements to the investigators from the Office of Management Assessment and communications from Dr. Sunderland's attorney to NIH were factually inaccurate or incomplete, especially statements relating to the nature of the Pfizer collaborations involving human tissue samples.

Discussion:

The Office of Management Assessment (OMA) of the NIH interviewed Dr. Sunderland regarding these matters on August 19, 2004. Dr. Sunderland signed the interview notes on August 31, 2004, confirming with an "X" that "[t]hese notes, with indicated changes, accurately summarize the interview." (Exhibit 14) Dr. Sunderland informed OMA that while he had taken the required ethics courses and understood there were rules governing disclosure of financial interests and approval of outside activities "he may not have paid proper attention" to such matters in the past. He maintained that he did provide the documents from which to complete the 520s (outside activity request forms) but that somehow the clerical staff did not make the necessary submissions nor did they inform him that such submissions were not made.

[15] According to Pfizer records, what remains of the samples represents about half of what was shipped by Dr. Sunderland. Pfizer is "happy to work with NIH to arrange the return of the samples." June 6, 2006 e-mail from Daniel Kracov, Esq. (outside counsel to Pfizer) to Committee staff.

With regard to his financial disclosure forms, Dr. Sunderland placed blame for at least part of their inaccuracy on his support staff. The OMA dismissed this argument: "Dr. Sunderland violated NIH and Commissioned Corps procedures and policies on multiple occasions (Pfizer reported 140 activities for which there were no approvals) all of which cannot be dismissed as administrative oversights or anomalies. Given that he acknowledges that he had concerns about administrative support, he should have ensured that forms were submitted to the NIMH ethics office and that approvals were given. Dr. Sunderland was aware of the NIH ethics process through ethics training and was ultimately responsible for ensuring that all activities were approved and all financial disclosures were made." (See Exhibit 32) Committee staff interviewed several individuals within the Geriatric Psychiatry Branch run by Dr. Sunderland and found no support for his position regarding clerical malfeasance.

When asked about his consulting conflicts of interest, Dr. Sunderland told OMA that "he had a consulting arrangement with Pfizer Corporate and the MTA with Pfizer researchers." In fact, not only was the MTA and his initial consulting agreements signed by the same Pfizer official, Dr. Barrie Hesp, both contracts covered work directly related to the samples initially supplied under the MTA. (Exhibit 13)

Dr. Sunderland further claimed that he sent human spinal fluid samples to Pfizer as he had to more than 30 other collaborators and that his collaboration with Pfizer would not have required visits to the company, as this was "an exchange of material for analytical data." In fact, records show that Dr. Sunderland and his associate Karen Putnam visited the Pfizer facilities on a number of occasions to work on the data and, according to Dr. Friedman, at least once Dr. Sunderland accompanied Friedman and the spinal fluid samples on a plane to OGS in England. In addition to the Friedman interview information and several e-mails discussing trips to Pfizer in relation to the unknown biomarker work, both Karen Putnam and Pfizer informed Committee staff that Pfizer considered the primary data associated with the unknown biomarker project to be proprietary and could only be accessed on Pfizer property. (Exhibit 33)

Another inconsistency with the relevant documents and the information conveyed by Pfizer regarding Dr. Sunderland's consulting activities was Dr. Sunderland's statement in the OMA interview that "his consulting work with Pfizer has to do with drug development and lectures." Certainly lectures to audiences of doctors arranged by Pfizer's marketing team charged with promoting Aricept accounted for substantial payments to Dr. Sunderland ($311,150 from 1996 to 2004 according to Pfizer) (Exhibit 34) The consulting work involving the human tissue samples, however, was separate and apart from those lectures. (Exhibit 34) To the extent Dr. Sunderland meant that his "drug development" consulting was drug-specific, except perhaps for participation on various Pfizer-sponsored Advisory Boards relating to marketing strategy, Committee staff found little evidence from records or interviews that Dr. Sunderland's consulting with Pfizer was related to any existing drug or drug under development. On the other hand, if Dr. Sunderland meant that his "drug development" consulting in a more general way applying to strategic advice to classes of medications, his attorney in a December 8, 2004, letter to NIH distinguished this general consulting from his work on the "unknown biomarkers" project: "Generating new approaches to shorten the duration of clinical

trials using various target markers is an obvious priority for companies like Pfizer, and Dr. Sunderland provided ongoing consultation about the development of such strategies. This consulting is quite different and separate from the exploration of *peptide biomarkers* for possible diagnostic and prognostic use in Alzheimer's disease."[16] (Emphasis added). Later in the same letter, Dr. Sunderland's attorney described a reason for the April 1998 MTA collaboration as "[p]roteomic exploration of CSF [cerebrospinal fluid] was designed to help discover *peptide targets* for drug development with both scientific and potential commercial applications."[17] (Emphasis added).

During much of the time period (1998-2004) of Dr. Sunderland's consulting with Pfizer, Ms. Karen Putnam was a 32-hour per week employee of NIMH assigned to Dr. Sunderland's branch, although she was telecommuting from the University of Cincinnati where she was pursuing a graduate degree. (See Exhibit 11) According to e-mails, Dr. Sunderland urged Pfizer to hire Ms. Putnam to administer the database related to the unknown biomarker project. Pfizer tightly held the data from this "collaboration" so her work on that database had to be done at the company. Ms. Putnam performed a similar function with regard to the "known biomarkers" database. She informed the Committee staff that she understood that while the "unknown biomarkers" project was covered by her consulting agreement with Pfizer, the work she and Dr. Sunderland did with Pfizer on known biomarkers was a part of her official duties. Both biomarker projects started with consulting contracts between Pfizer and Dr. Sunderland, not independently and solely from NIH.

During his OMA interview Dr. Sunderland was asked whether he told Karen Putnam that she did not have to seek approval for her work with him at Pfizer. In the signed interview notes Dr. Sunderland claimed not to remember if he told Ms. Putnam not to file, but he went on to state that he did not think she had to because she was a part-time employee on an IPA and because "her duties did not overlap with any decisions regarding drug or protocol development." Ms. Putnam was a direct report to Dr. Sunderland and had received almost $65,000 in consulting fees and expenses from Pfizer to manage the data of the unknown biomarker study. (Exhibit 39). OMA found, and Ms. Putnam confirmed, that she had not submitted requests for outside activities. Exhibit 11. In addition, the NIH ethics review panel concluded that had Karen Putnam filed a request for outside activity the request would have been denied because it related to her official duties. (Exhibit 27) OMA noted in its review of Karen Putnam's outside activities that in an e-mail to Ms. Putnam, dated June 18, 2004, the NIMH Ethics Coordinator stated that Dr. Sunderland had called from abroad to say that he had advised Ms. Putnam that she did not have to file for prior approval.

Dr. Sunderland's attorney in an August 31, 2004, letter to OMA stated: "There was no conflict between his consulting/lecturing and his clinical work at the NIH. . . "[He] never hid that relationship; and that there never was a conflict of interest – in any respect whatsoever – between his NIH work and what he did as a consultant and speaker

[16] December 8, 2004, letter from Robert F. Muse, Esq. to Holli Beckerman Jaffe, Director, NIH Ethics Office, page 7.
[17] Id. , page 8.

for Pfizer. . . . The relevant facts are now before the NIH in their entirety." The NIH Ethics Review Panel specifically found that there was "a direct overlap between the subject matter of Dr. Sunderland's official area of research and the scientific subject matter of his Pfizer consultancies." (Exhibit 35) He would not have been "given prior approval for the consultant activities." The Ethics Panel "expressed further concern over the Material Transfer Agreement (MTA) that Dr. Sunderland entered into with Pfizer in 1998 while he maintained an ongoing consulting relationship with the company in the same area." Based on records and interviews, Committee staff believes that NIH did not conduct interviews with Pfizer employees nor obtain from Pfizer the underlying records of Dr. Sunderland's consulting agreements. Thus, even without the Pfizer documents and interviews that show connections between the MTA and the consulting, the Ethics Review Panel still concluded in April 2005 that there was a conflict of interest.

Moreover, OMA believed that Dr. Sunderland did much of the Pfizer-paid work on government time. Dr. Sunderland acknowledged in the OMA interview that he never kept track of his leave time nor, as her supervisor at NIH, did he check to see if Ms. Putnam had taken leave when he signed her time cards.

Records and interviews also raised questions about Dr. Sunderland's openness about the "unknown biomarkers" consulting agreement involving a third-party British company called OGS. For example, in her June 9, 1998, e-mail, Kathryn Smith noted to other Pfizer officers: "For your information, Dr. Trey Sunderland at NIH (our source for the AD samples) has requested that we do not mention him in any publicity concerning his involvement in our OGS collaboration." (Exhibit 23). In addition, when the Committee first raised questions about the discrepancies involving Dr. Sunderland's outside activities with Pfizer, the NIMH ethics coordinator in a June 18, 2004 e-mail to Dr. Sunderland asked directly: "There is a record of an MTA agreement with Pfizer signed 4/98. Could payments have related to that?" (Exhibit 16) Based on records and interviews, there is no evidence that Dr. Sunderland responded to this question. It should also be noted that the terms of Dr. Sunderland's consulting agreements state: "Pfizer agrees that it will not make public this agreement nor the terms associated with it."

Dr. Trey Sunderland is still an employee at the NIMH and is a member of Public Health Service Commissioned Corps. Administrative action rests with the Corps and not NIH per se. Dr. Thomas Insel, the Director of NIMH, forwarded a summary of the OMA findings and those of the Ethics Panel to the Commissioned Corps, noting that he was informed that civilian employees guilty of the same violations would be proposed for removal. In relevant part that document states:

> "Dr. Sunderland placed the NIH in a position where it had to respond to allegations of impropriety, which compromised faith in the Agency and trust in our research.
> Dr. Sunderland violated ethics rules with regard to his relationship with Pfizer and engaged in relationships with Pfizer and many other organizations that would not have been approved had he submitted them for approval in accordance with the process for seeking approval of outside activities…Not disclosing over $500,000 in income was not an oversight or lapse in judgment but appears to be a deliberate

decision not to comply with the rules, policies and procedures that are necessary to protect the NIH, its scientists and most importantly, its science."

Question Three: Did the Committee's investigation of the circumstances surrounding Dr. Sunderland's transfer of human samples to Pfizer identify evidence that raised other compliance issues and policy questions?

Finding/ Supporting Evidence: Yes. The investigation found reasonable grounds to believe there was questionable compliance with human subject protection and NIH technology transfer policies that existed at the time. The evidence also raised regulatory and ethical questions that are pertinent to NIH's consideration of current policy related to human tissue samples.

Discussion:

Human subject protection

A human subject is a living individual about whom a researcher (called an investigator) obtains either (1) data through intervention or interaction with the individual, or (2) identifiable private information.[18] In the case study before the Subcommittee, Dr. Sunderland and other researchers collected spinal fluid by injecting the human subject with a needle at the base of the spine in a procedure called lumbar puncture (LP). According to the informed consent language in several of the protocols involved, this procedure is conducted in the morning, after the subject has had a night of bedrest. The subject lies on one side, the subject's lower back is cleaned with antiseptic, and a local anesthetic such as novocaine is injected in order to temporarily numb a small area of skin. A needle is then placed into the spinal fluid sac, allowing an ounce of spinal fluid to drip into collection tubes. The needle is then removed and the subject is asked to lie on her/his abdomen for three hours to reduce the likelihood of developing a headache after this procedure. The LP procedure only takes 5-15 minutes. Most subjects experience only minor or moderate pain, similar to that experienced when an injection is received.

The spinal fluid samples, usually collected in 20-30 cc amounts, are then alliquotted or subdivided into ten smaller tubes. Some small subset of the total amount is then used for the research study, with several other vials or test tubes of fluid left over, unused, stored in –70 degree centigrade freezers.

Researchers at the NIH are responsible for protecting the rights and welfare of the human subjects who participate in their research. All intramural researchers at the NIH are responsible for knowing whether or not their research involves human subjects. Thus, legal obligations to protect human subjects apply to human tissue samples and private information, such as medical information, that can be readily identified with individuals.

[18] Title 45 Code of Federal Regulations, Part 46.

a. Questionable handling of informed consent. One issue presented by this matter involves the adequacy of informed consent for new, future uses of leftover human samples. The ethical foundation for informed consent is the principle of respect for persons, which requires that research subjects be given the opportunity to choose what shall and shall not happen to them.[19] Valid informed consent requires disclosure of relevant information about the research, comprehension of the information by the prospective subject, and his or her voluntary agreement, free of coercion and undue influence, to participation.[20]

In this case, Dr. Sunderland transferred spinal fluid samples to Pfizer that were collected from subjects whom most were told of the specific purpose of the particular research study being conducted, but not about the research purpose of the Pfizer collaboration, because in many cases that collaboration had not yet even been developed. At the time of collection, many of the spinal fluid samples were not obtained for the research purpose of the Pfizer collaboration. In general, there is a question about whether most of the protocols at issue had adequate informed consent language about consenting for future research uses of leftover samples.[21] A few of the protocols involving the subjects are still ongoing and Dr. Sunderland actually sought Institutional Review Board (IRB) approval for amending these ongoing protocols to reflect the new research purpose involving Pfizer.

Human subject protection regulations, however, state that unless the samples are anonymized and not linked to identifiable patients, the human tissue samples are not exempt from IRB review and some independent review (either from the IRB or the human subjects protection office of the institute or center) must be conducted to determine if full IRB review is needed and if so, whether the subjects need to be consented again for the new use.[22] With respect to the samples transferred to Pfizer, NIH

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[19] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles for the protection of human subjects of research. Washington, D.C.:Government Printing Office, April 18, 1979. U.S. Department of Health and Human Services publication GPO 887-809.

[20] Position Statement, The Ethics and Humanities Subcommittee of the American Academy of Neurology, Neurology 1998, 50: 592-595.

[21] That silence or ambiguity would not have been unusual for most clinical research protocols because there had been no requirement to address future uses. It was not until January 2006 that the NIH Office of Human Subjects Research (OHSR) explicitly addressed this issue, revised its guidance, and issued "Sheet 14 Guidance on the Research Use of Stored Samples or Data." In that guidance, researchers are required to submit a written protocol to an NIH IRB that includes a description of how samples will be tracked, how samples will be stored to be protected from loss or destruction, plans for samples at the conclusion of the protocol, and what circumstances would cause the lead researcher to report a loss or destruction of samples to the IRB. In discussion with Committee staff, the NIH Deputy Director of Intramural Research, whose office includes OHSR, stated that this revision occurred in response to the Committee's investigation.

[22] David B. Resnik, J.D., Ph.D., National Institute of Environmental Health Sciences (NIEHS) Bioethics Bulletin, "Human Research Q&A," Spring 2005, at 2:

Question: "I have access to some leftover tissue samples from another investigator's work. I would like to conduct some research on these samples. Is this research on a human subject? Do I need to submit a protocol to the NIEHS's Institutional Review Board (IRB)?
Short answer: This is not research on a human subject but you still need to contact the IRB before using these samples in research, since the samples were taken from human subjects."

reported to Committee staff by e-mail that "[n]either the NIH OHSR [Office of Human Subjects Research] nor the NIMH [Institutional Review Board] have records documenting a review of the transfer to Pfizer." According to NIH, "Dr. Sunderland has advised NIH that he believed at the time of the transfer that use of specimens in his collaboration with Pfizer, as described in the 1998 MTA, was completely consistent with both the protocols in which those samples were obtained, and the informed consent documents signed by participants."

But was it Dr. Sunderland's judgment alone to determine whether the use of the samples was consistent with the protocols? Under the April 1995 Guidelines for the Conduct of Research Involving Human Subjects in effect at the time of the 1998 transfer, the use of human tissue samples were exempt from the NIH requirements on human research protection if the sources of pathological specimens "cannot be identified directly or through identifiers linked to the subjects." The Guidelines also state in bolded print: "Investigators should not make determinations about exemptions without consulting OHSR."

The terms of 1998 Material Transfer Agreement (Exhibits 2 and 3) and the records produced by Pfizer relating to the samples provide reasonable grounds to believe that Dr. Sunderland intended to transfer, and actually transferred, coded clinical samples to Pfizer. Coded clinical samples are specimens supplied with a code rather than a name or social security number. Because these samples remain linked through codes to identifiable subjects, questions are raised over whether these samples would have been covered by human subject protection guidelines and whether Dr. Sunderland should have sought an independent consultation or determination.[23] Currently, in light of concerns raised by the Committee's investigation and at the direction of the NIH Deputy Director for Intramural Research, an NIH investigation is being conducted to determine if Dr. Sunderland violated any regulatory or ethical standards in transferring spinal fluid samples to Pfizer without any IRB review from protocols that did not cover the research purpose in the Pfizer biomarker projects.

b. Inadvertent disclosure of subject names and other privacy information. In reviewing records produced by Pfizer, Committee staff found that February-March 1999 spreadsheet records for assays of two different potential biomarkers in 1999 contained the names of approximately 120 subjects who were the sources of the biological material, along with their codenames, NIH ID numbers, dates of birth, race, and sex. In consultation with Pfizer's outside counsel, Committee staff confirmed that these records did indeed represent an inadvertent disclosure of subject names. According to Pfizer's outside counsel in a March 31, 2006, letter to Committee staff, the spreadsheets contained information transcribed by Pfizer from labels on the vials sent by the NIMH. The

[23] After several months of inquiries by Dr. Molchan, Dr. Sunderland sent 0.5 cc paired spinal-fluid samples from eight Alzheimer's disease patients and two elderly normal volunteers to an outside researcher. In his interview with Committee staff, the Director of NIMH raised the issue of whether this transfer was in compliance with NIH guidelines along the same lines that questions had been raised by Dr. Sunderland's transfer of samples to Pfizer. Dr. Molchan, however, told the Committee staff that the research purpose of the outside researcher was the same purpose (to conduct a lithium study) in the study she had not been able to complete.

samples were subsequently coded by Pfizer for analysis using the first three letters of the patient's last name followed by the first three letters of the first name. The results of the study were included in the April 23, 2003, article in the Journal of American Medical Association as well as the analysis of a later set of samples. Subsequent samples arrived from the NIMH pre-coded using a numerical coding system.

In response to the Committee staff's question about Pfizer's handling of this inadvertent disclosure, Pfizer's outside counsel wrote:

"At the time that the NIH disclosure occurred, the Health Insurance Portability and Accountability Act (HIPAA), which established requirements regarding the use and disclosure of Protected Health Information, was not yet in effect, and thus there was no legal obligation imposed upon Pfizer to return or reject the information received. Even under the current HIPAA requirements, Pfizer's research and development organization is not a 'covered entity,' and the duties imposed on such persons inadvertently receiving protected information are not clear. However, we believe Pfizer handled the inadvertent disclosure appropriately by creating an [sic] code to de-identify patients in the course of the research effort."[24]

There is no evidence that Pfizer contacted NIH about the inadvertent disclosure. There is no evidence that NIMH was aware of the inadvertent disclosure. If that was the case, NIH had no information to determine what led to the inadvertent disclosure, and was not in a position to correct a possibly recurring, systemic problem that increases the risk of inadvertent disclosure of privacy information. Further investigation would be needed to determine the circumstances that led to the inadvertent disclosure.

Committee staff understands from a discussion with NIH Acting Director for Human Research Protection that the release of patient names, whether accidental or not, is not consistent with NIH research standards and any manuscript in connection with the affected research project might not be published. This would need to be reported to the IRB, and to the NIH Deputy Director for Intramural Research. The NIH Deputy Director in turn might report this disclosure to the Office of Human Research Protection.

c. Questionable non-disclosure of financial relationship to IRB. As part of his financial arrangement with Pfizer, Dr. Sunderland transferred spinal fluid samples to Pfizer from 1998 to 2004 for which he was paid $285,000 to advise Pfizer on data relating to the samples provided. According to NIH records, Dr. Sunderland provided spinal fluid samples that had been collected from 14 different studies.[25] Two of these studies were initiated in 2001 and 2002, respectively. In other words, Dr. Sunderland was performing lumbar punctures for spinal fluid at a time Pfizer wanted spinal fluid samples, and at a time Dr. Sunderland sought and received monetary compensation for his efforts to assist Pfizer in interpreting data generated from these spinal fluid samples

[24] Letter dated May 10, 2006, from Daniel A. Kracov, Esq., Arnold & Porter (on behalf of Pfizer, Inc.) to Committee staff.

[25] The NIH recently advised the Committee staff that the internal NIH investigation on human subject research issues had identified 16 different studies connected to Dr. Sunderland's transfer of human samples to Pfizer.

he provided. In addition, while other studies no longer involved active collection of spinal fluid, these studies were still ongoing and were subject to continuing review by the NIMH IRB. As part of this continuing review process, Dr. Sunderland as the accountable investigator on the study had to check off "yes" or "no" responses to a series of questions on the NIH-1195 form, Clinical Research Protocol Continuing Review Application. The last question on the form was: "Have any investigators developed an equity or consultative relationship with a non-NIH source related to this protocol which might be considered a conflict of interest?" According to all forms related to spinal fluid protocols signed by Dr. Sunderland during the time he was consulting with Pfizer, the "no" box response was checked. (Exhibit 24)

Committee staff did not receive any records that linked the individual samples provided to Pfizer to specific protocol numbers. The 2001 study and the 2002 study, however, were identified as sources of spinal fluid samples to Pfizer. (Exhibit 26) Thus, while the Committee staff does not believe it has records linking the protocol number to a particular NIMH shipment to Pfizer, samples were provided to Pfizer from these studies in one of those years in which Dr. Sunderland represented to the IRB that he (or any other investigator associated with the study) had no outside financial interests related to the protocol.

d. Cancellation of lithium study without notice to subjects. Dr. Molchan left NIMH in early 1997. By that time, Dr. Molchan had completed the spinal fluid collection phase of the lithium study a few years earlier. She was still, however, conducting the study and had used only a relatively small percentage of the samples.

Committee staff understands that sometimes when an NIH scientist in charge of a human subjects study leaves NIH, another NIH scientist is assigned to take charge of the study and the study is continued.[26] When Dr. Molchan left NIMH, there was reason to believe (IRB approval, two papers published) the lithium study would be continued and that Dr. Sunderland as Branch Chief would either take over the study or assign someone to take over the study. Instead, the study was discontinued. Committee staff has asked NIH why the study was discontinued. To date, NIH has not provided a response on why this study was discontinued.

Committee staff has not found any evidence that the subjects in the lithium study were notified about the termination of a study. In these cases, where a clinical trial is terminated, the question is raised whether the subjects in that study should be notified of the termination. It is unclear how common it is for the written protocols of the clinical trial to include provisions about termination and notification. On the question of when a subject should be notified about termination of a study, an NIH official with expertise on human subjects protection told Committee staff that she believed that it depended on whether the study followed the subjects over a period of time. Nevertheless, the NIH Office of Intramural Research is working on a computer consent prototype and whether it should be a standard requirement to inform subjects of a study's termination.

[26] For example, in 2005 Dr. Robert Cohen took over as the Principal Investigator for Dr. Sunderland in a few of the protocols involved as sources of spinal fluid for Pfizer.

Technology Transfer Issues

In pursuing its mission, NIH scientists often discover new technologies. The process of sharing these new technologies with other organizations and the public is called technology transfer. For example, the sharing of new research materials with colleagues, the pursuit of collaborative relationships with outside entities, and the awarding of intellectual property rights to commercial entities for development and commercialization, are all considered technology transfer activities. The NIH Office of Technology Transfer is responsible for developing and implementing technology transfer policies at NIH. Each Institute has a technology transfer office that monitors, evaluates, and manages the Institute's invention portfolio. These offices review Employee Invention Reports (EIRs) and negotiate transactional agreements between the Institute and outside parties, including other Federal laboratories, State and local governments, universities, and pharmaceutical and biotechnology companies. Among these agreements are Material Transfer Agreements (MTAs) for the exchange of research materials, and Cooperative Research and Developments Agreements (CRADAs) for collaborative research endeavors.

In this case, questions are raised in a number of areas about how NIMH at the time implemented technology transfer policies and the adequacy of certain technology transfer policies.

a. Improperly authorized transfer. The transfer of spinal fluid samples was facilitated by the April 1998 Material Transfer Agreement between NIMH and Pfizer. The Committee's investigation found two versions of the executed MTA. One version contained the signature of Dr. Sunderland as the provider of the samples on behalf of NIMH and the signatory for Pfizer, Dr. Barrie Hesp. (Exhibit 3) This is the only version of the MTA that Pfizer told the Committee staff it has. Committee staff found no evidence that Pfizer had any other version of the MTA. According to a Pfizer manager involved with the MTA, Pfizer made an effort to confirm that Dr. Sunderland had the authority.[27] A March 1998 Pfizer e-mail does substantiate phone contact between the Pfizer manager and the NIMH technology transfer director about the MTA.[28] Although she did not have specific recollection about the Pfizer phone call, the NIMH technology transfer director at the time (who has since left the NIH) told the Committee staff that she recalled getting phone calls about MTAs. These would not have been calls to receive

[27] May 10, 2006, letter from Daniel Kracov, Esq. to Committee staff: "In April 1998, what was Pfizer's understanding of Dr. Sunderland's authority to sign an MTA? In 1998, Pfizer sought to confirm Trey Sunderland's authority to enter into the MTA on behalf of NIH. In this regard, Pfizer's Kathy Smith was referred to Kathy Conn at NIH [the NIMH Director for Technology Transfer] who, to Kathy Smith's recollection, confirmed that Dr. Sunderland was authorized to execute the agreement. It has been Pfizer's standard practice when dealing with academic institutions, including institutions such as NIH, not to accept an investigator's claim to have authority to sign an agreement without consulting with an appropriate representative of the contracting institution."

[28] E-mail from Kathryn E. Monaghan [Smith] to Trey Sunderland, March 24, 1998: "Trey, I spoke with Kathy Conn today and she also reconfirmed that we can proceed with the MTA immediately and work out the CRADA vs. Consult part in due course. I fedexed various forms of the MTA on Friday -- hope you got them yesterday?" Exhibit 31.

official clearance but just preliminary inquiries. These kinds of calls were not documented. According to the official, she believed the Pfizer inquiry would have been about what form to use in transferring samples to Pfizer. She did not know that Dr. Sunderland and Pfizer were executing the MTA immediately. She expected to see the MTA and review it. There is, however, no evidence showing she received any Pfizer correspondence and was sent the MTA. She had no recollection about any mention of possible consulting, but even if it had been mentioned, she would have expected the ethics office to be involved in that review. The official disputes that she confirmed that Dr. Sunderland was authorized to execute the agreement. Based on the phone call, the official expected to review the MTA and forward it to the NIMH Scientific Director for signature. The official's recollection was that all transfers of human tissue samples to researchers outside NIH were documented through MTAs.

In early 1999 during an office move, the NIMH technology transfer office staff discovered a number of MTAs that had not been co-signed by the NIMH Scientific Director, as required by the written delegations of authority in effect at the time. One of these MTAs was the Sunderland-Pfizer MTA. When these MTAs were brought to his attention, the NIMH Scientific Director co-signed. He co-signed the Pfizer MTA on February 24, 1999. At that time, NIMH had already made three shipments of spinal fluid to Pfizer. (Exhibit 3, p.3) The co-signed MTA was retained in NIMH files. According to NIH, there was no evidence that Dr. Sunderland was given a copy of the 1998 MTA after Dr. Desimone signed, and Dr. Sunderland told NIMH he did not get a copy of the co-signed MTA until about several months ago when he requested it from the NIMH Executive Officer.[29] Moreover, it is unknown when Dr. Sunderland learned about the existence of the co-signed MTA.

The available evidence shows that Pfizer only had the MTA with Dr. Sunderland's signature. Under NIMH policy at the time, however, Dr. Sunderland was not the authorized signatory to execute the MTA. Questions arise about whether NIMH's transfer of samples was legally authorized and the legal implications for NIH. Furthermore, available evidence shows that NIMH management did not provide the co-signed versions to either Dr. Sunderland or Pfizer. This is of concern because NIMH management should have an interest in correcting an internal problem of unauthorized or improperly authorized material transfers. The problem cannot be corrected if management does not make NIH scientists aware of the error. In a conversation with Committee staff, the former NIMH technology transfer director acknowledged that this was an oversight.

b. Plasma samples transferred without MTA. According to records from Pfizer and others, NIMH shipped 388 plasma samples to Pfizer on August 19, 2002. The Committee has no records of a material transfer agreement covering these plasma samples. The April 1998 MTA and the October 6, 2000, amendment to this MTA only covered coded clinical samples of spinal fluid and serum.[30]

[29] E-mail from Gemma Flamberg (NIH) to Alan Slobodin (Committee staff), June 1, 2006. (Exhibit 37)

[30] Pfizer, however, did not actually receive any serum from NIMH (March 31, 2006, letter from Daniel A. Kracov, Esq. to Committee staff).

c. Questionable amendment to MTA. The April 1998 MTA was executed using the Public Health Service Agreement MTA form and Dr. Sunderland was listed as the provider at his NIMH address. The October 6, 2000, amendment to the April 1998 MTA was executed on Pfizer letterhead and listed Dr. Sunderland at his home address. Committee staff asked NIH whether there were any amendments to the 1998 Pfizer MTA. NIH told the Committee staff that the NIMH Technology Transfer Office did not have an amendment but then NIMH asked Dr. Sunderland if there had been any amendments. At that point, Dr. Sunderland produced the October 2000 amendment. In an interview with Committee staff, the NIMH Technology Transfer Director stated that this amendment "would have raised eyebrows." Even though NIH told the Committee staff that Dr. Sunderland had the signatory authority to execute an MTA in 2000, because Dr. Sunderland had executed the MTA and had it co-signed by the NIH Scientific Director, the same process of authorization in effect in 1998 should have been used for the amendment in 2000.

d. NIMH policy on MTAs lacked basic controls of accountability. According to an NIH e-mail to Committee staff, Dr. Sunderland had the authority to transfer the spinal fluid samples to Pfizer on his own without any approval or reporting, as long as Dr. Sunderland chose not to document the transfer without an MTA. Because he chose to execute an MTA, however, he did not have authority on his own to provide the samples. He needed clearance from the NIH Scientific Director. In other words, NIMH policy at the time, as represented by NIH, gave scientists more authority to provide government property to non-government researchers without any paperwork than if the scientists chose to do the paperwork. This kind of system raises the question whether such a policy incentivized a lack of accountability.

Moreover, in 1999 the NIMH changed its written delegations of authority to permit Branch Chiefs, such as Dr. Sunderland, to have sign-off authority on MTAs. The stated rationale was to ensure that branch chiefs were aware of what materials were coming and going from the labs under their supervision. According to NIH in an e-mail to Committee staff, Dr. Sunderland had the authority after May 24, 1999 to approve his own transfers of material (including human tissue samples) outside NIH. This NIMH policy, or perhaps policy interpretation, raises the question about the lack of essential checks and balances to protect against fraud and error because the Branch Chief could approve his own MTAs for samples from studies in which he was involved as the Principal Investigator.

e. Lack of clarity in NIMH policy on MTAs. Committee staff found an information bulletin, “NIH Technology Transfer and You,” posted on the NIMH Technology Transfer Office (TTO) web site. The bulletin stated that that the NIMH version was revised on February 24, 2000. This bulletin stated in boldface type:

Current NIH policy requires that MTAs be used whenever an NIH scientist sends out or receives materials, e.g., cDNAs, cell lines, antibodies, etc. These agreements must be signed by authorized IC personnel.[31]

The NIMH TTO Director at that time told Committee staff in an interview that MTAs were required. Other NIMH officials and NIH, however, disputed that the policy was so clear-cut. Rather, scientists were encouraged to use MTAs but not required to do so. In other words, MTAs were discretionary. NIMH officials interviewed by Committee staff also were not familiar with the TTO Bulletin. This area raises a question about the adequacy and accuracy of internal communication at NIMH. There is also a question about what was the actual policy.

f. The MTA was a questionable mechanism for the transfer. Committee staff obtained records showing that Dr. Sunderland was the provider of spinal fluid samples in a 1989 Cooperative Research and Development Agreement (CRADA) between NIMH and Abbott Laboratories. Under this CRADA, Dr. Sunderland provided 115 samples of spinal fluid to Abbott. NIH and NIMH officials could not distinguish between the Abbott transfer and the Pfizer transfer in terms of why a CRADA was used with the transfer to Abbott but not with the one to Pfizer in 1998. Moreover, at a 1999 NIH Conference on Biomarkers, Dr. Sunderland stated: "In a large-scale *collaboration* between the NIMH, Pfizer, and OGS, we have embarked on a series of studies focused on one very important part of biomarker puzzle," and later stated that "cerebrospinal fluid markers are the focus of our *collaborative* efforts with Pfizer and OGS."[32] (Emphasis added). Given such characterizations[33]of the activity with Pfizer and OGS as well as other information, these officials believe that Dr. Sunderland and Pfizer were in fact engaged in a collaboration in which a CRADA would have been the appropriate mechanism to use.

g. Reference to third-party collaborator in MTA should have triggered more scrutiny. Provision #2 in the April 1998 MTA stated that: "The Research Material will only be used for research purposes by Recipient and Recipient's collaborator in the UK, for the research projects described below, under suitable containment conditions." The mention of the Recipient's collaborator in the UK was a reference to Oxford Glycosciences, Ltd., (OGS), as part of the collaboration with Pfizer. OGS was part of the three-way collaboration with Pfizer and NIMH. OGS used 2D gel electrophoresis techniques to detect proteins in spinal fluid. OGS was not, however, specifically identified in the MTA. The involvement of a third-party collaborator raises a question of whether this was a modification of a routine material transfer and should have triggered further scrutiny from the Technology Transfer Office. The question is raised about whether uses and recipients of samples are adequately reported in the MTA and whether NIMH should have been made more aware of OGS and the use of the samples. Moreover, the MTA authorized the transfer of spinal fluid samples for the narrow

[31] (Exhibit 38)
[32] T. Sunderland, "Prospective search for Alzheimer's disease (AD) biomarkers," in Downing, ed., Biomarkers and Surrogate Endpoints: clinical research and applications, Proceedings of the NIH-FDA Conference held on 15-16 April 1999 in Bethesda, Maryland, USA, at 39, 40 (Elsevier, 2000).
[33]Dr. Sunderland also highlighted this collaboration in a paper he prepared for a 2000 NIMH of Board of Scientific Counselors review of research in his branch.

purpose of the collaboration, which Pfizer refers to as the "unknown biomarker" projects. Records, however, produced to the Committee show that Dr. Sunderland provided over 2,100 samples to Pfizer for the "known biomarker" project. OGS, however, was not involved in this collaboration and it was actually a separate biomarker research project. A question is further raised whether the 2100 samples sent to Pfizer for this project were entirely unauthorized.

h. Most of the samples transferred to Pfizer may not have been covered by the MTA and the MTA amendment. As mentioned before, the terms of the MTA related to transfers for the research purpose of the three-way collaboration of NIMH, Pfizer, and OGS. Pfizer calls this collaboration the "unknown biomarkers" project. The second project between Dr. Sunderland and Pfizer, did not involve OGS and Pfizer calls this "the known biomarker project." The NIH documents produced to the committee relating to the Pfizer collaboration state that the total number of samples sent to Pfizer equals 2132 vials for beta-amyloid 1-42, beta-amyloid 1-40, and tau. These are known biomarkers and relate to the "known biomarker" project. One of the NIH documents asserts that the samples sent to Pfizer were "through the NIH-approved MTA." The Committee, however, has not received any records of any MTA covering the known biomarker project. It is highly questionable whether NIH technology transfer and legal officials would find that the April 1998 MTA for the unknown biomarker project could be used to authorize transfer for the known biomarker project, even though it involved the same company and the same area of research, because the samples were used for a different research purpose.

Science management concerns

Three important concerns were raised: lack of retention of clinical research data, conflict of interest in committing NIH scientific resources, and NIH oversight of unpublished research.

a. Lack of retention of clinical research data. When Dr. Molchan inquired about getting the leftover spinal fluid samples, she also asked about getting the data from her uncompleted lithium study. Dr. Sunderland informed Dr. Molchan that this data was no longer available:

"Dear Sue,

Over the last few days, we have been searching electronic files and paper files to see what we could find. Unfortunately, the data is no longer available. Just so you know, we had to go through several purges over the last few years when we moved offices, and anything over 5-7 years old was subject to purging. Since these studies and the resultant publications go back over 15 years in some cases, they were not carried forward to our limited space. . . . " (Trey Sunderland e-mail , March 14, 2005 to Susan Molchan).

Dr. Molchan raised the issue of data retention in an e-mail to Committee staff: "Does NIH have a policy on what happens to data like this when scientists leave the NIH? It seems wasteful to repeat the same studies without having earlier results."

Two senior NIH officials provided somewhat conflicting information. One official confirmed the policy of purging clinical data after seven years. Another official, however, had never heard of such a policy. The Subcommittee may wish to raise this question with NIH about what the policy is, and what the policy should be, on retention of clinical research, particularly in cases where the researcher has left NIH.

b. Commitment of resources. Dr. Sunderland's collaborations with Pfizer resulted in the shipment of over 3,000 spinal fluid and plasma samples. These samples were extraordinarily valuable, both scientifically and commercially, because they contained useful information, they were linked to well-characterized clinical data (lots of medical details about the subjects), and the samples were taken from these same subjects over different points in time over several years. The Committee staff could find no evidence that showed in 1998 any NIMH official besides Dr. Sunderland who was even aware, much less supportive, of the merits of the Pfizer collaboration. Thus, Dr. Sunderland, while having concurrent financial interests with Pfizer, made the decision to commit 3,000 non-renewable taxpayer-supported human research samples.

Techniques employed in proteomic analysis are new and evolving. Even if Dr. Sunderland may have been the scientist in the best position to evaluate whether the OGS technology was promising enough to consume these valuable human tissue samples, the intramural research program at NIMH or NIH may have had more than one expert in proteomics to assist in such a decision. Could Dr. Sunderland's scientific judgment have been better informed by consultations with other proteomic experts at NIH? The Pfizer projects may have been the most promising collaboration available in the search for biomarkers of Alzheimer's disease. Could an exploration of other private sector or academic partners produced a more promising result? Most importantly should a single scientist be the sole decisionmaker about the best use of these unique human tissue samples, especially with direct financial interests involved?

c. NIH oversight of unpublished research. In the year 2000, Dr. Sunderland prepared a document called "Overview - GPB," in preparation for a review by the NIMH Board of Scientific Counselors. On page 3 of this document, the discussion about the Pfizer/OGS collaboration is as follows:

"Perhaps the most interesting interaction is the three-way collaboration between the NIMH, Pfizer, Inc., and Oxford Glycosciences in England. This cooperative approach was first established in 1998 to investigate protein spots in the CSF of AD subjects and 'at risk' controls at baseline and over time. While this convergence of government investigators, the pharmaceutical industry, and a biotechnology firm has been highlighted by the NIH Director at a recent national biomarkers meeting as a way to leverage resources and scientific interest in the future, the proof of its power must come from the data, especially over time. Using high-throughput, exquisitely sensitive 2D gel electrophoresis techniques which provide quantitative data reflecting the up- and down-regulation of proteins in human CSF, we are generating cross-sectional data on over 1200 proteins in groups of AD and 'at risk' subjects. Perhaps most importantly, we will have

longitudinal data in both these groups through repeat CSF collections that will allow us to track protein changes through the evolution of this illness."

Under normal circumstances, the BSC would have been scheduled for another review of Dr. Sunderland's work in 2005. However, because in late 2004, NIMH officials believed that Dr. Sunderland was going to be leaving the NIH the BSC review was cancelled. The Committee staff has not found any publications related to the Pfizer/OGS collaboration. When asked by Committee staff to retrieve data or some kind of workproduct that resulted from this collaboration, NIH was unable to do so. In an interview with Committee staff, Karen Putnam indicated that all data related to the unknown biomarker project was maintained on-site at Pfizer. As Ms. Putnam noted in her December 7, 2004, letter to NIH:

"Pfizer asked me to consult in the fields of statistics and data management. I was involved in specific projects exploring proteomics and statistical methodology. The Pfizer activities centered around discovery research, where the results were used to generate future hypotheses and directions of research. The results generated from my Pfizer outside activities were not part of the data involved in my current government job. All proteomics data were confidential and kept at the Pfizer site. The computer software and hardware used in exploring proteomics data was located at the Pfizer site."

Outside counsel to Pfizer confirmed to Committee staff that this was essentially correct. Thus, the available evidence is that the unknown biomarkers project (or "discovery research" per Ms. Putnam) did not generate data that came into possession of the NIH. Under these particular circumstances, NIH was unable to report to the Committee what this collaboration had produced for NIH's scientific research program.

Conclusion

In sum, the records and interviews conducted in this investigation raise serious questions of misconduct in connection with, and inadequate oversight and control over, human tissue samples in NIH intramural programs. It should be noted that the Committee staff found no evidence that Pfizer had any knowledge relating to the questionable conduct of Dr. Sunderland in connection with the April 1998 MTA and the subsequent shipments of samples. Members of the Subcommittee may wish to pursue these questions at the hearing with witnesses and/or other appropriate action.